Clinical trial results:
A Randomized, Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Pharmacokinetics and Antiviral Activity of Multiple Doses of Orally Administered ALS-008176 Against Respiratory Syncytial Virus Infection in the Virus Challenge Model

Summary

EudraCT number	2013-004036-30
Trial protocol	GB
Global end of trial date	18 June 2014

Results information

Result version number	v1 (current)
This version publication date	09 September 2016
First version publication date	09 September 2016

Trial information

Trial identification

Sponsor protocol code	ALS-8176-502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02094365
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alios BioPharma Inc
Sponsor organisation address	260 E. Grand Ave, San Francisco, United States, CA 94080
Public contact	John Fry, Alios BioPharma Inc, jfry7@its.jnj.com
Scientific contact	John Fry, Alios BioPharma Inc, jfry7@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2014
Global end of trial reached?	Yes
Global end of trial date	18 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the antiviral effect of oral ALS-008176 compared to placebo after inoculation with Respiratory Syncytial Virus (RSV-A) Memphis 37b virus.

Protection of trial subjects:

The safety assessments included clinical laboratory tests (hematology [including coagulation], serum chemistry, creatine kinase, and urinalysis), electrocardiogram, Spirometry, Complete physical examination and vital signs. Adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	62
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 303 subjects were screened . Of these, 64 were inoculated with challenge virus and randomized to receive study medication. Of the 64 subjects 62 were included in the Intent to Treat (ITT) population set.

Pre-assignment

Screening details:

Participants administered a nasal inoculation of RSV-A Memphis 37b virus on Day 0, monitored from Day 2-5 for presence of RSV infection. 12 hours after participants confirmed to be RSV positive they randomized, administered first dose of drug. Any subjects who were not PCR positive by evening of Day 5 were randomized, started treatment on Day 6.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants administered with Placebo oral solution for every 12 hours.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants administered with Placebo oral solution every 12 hours.

Arm title	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD

Arm description:

Participants administered with ALS-008176 oral-liquid suspension as a 750 milligram (mg) loading dose (Dose 1), followed by 500 mg every 12 hours (Q12) maintenance dose (Doses 2-10) under fed condition.

Arm type	Experimental
Investigational medicinal product name	ALS-008176
Investigational medicinal product code	
Other name	C12041850-E
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants administered with ALS-008176 as a 750 milligram (mg) loading dose (Dose 1), followed by 500 mg every 12 hours (Q12) maintenance doses (Doses 2-10) orally in the form of suspension.

Arm title	ALS-008176: 375 mg

Arm description:

Participants administered with ALS-008176 oral-liquid suspension, 375 mg every 12 hours for 5 days (10 doses) under fed condition.

Arm type	Experimental
Investigational medicinal product name	ALS-008176
Investigational medicinal product code	
Other name	C12041850-E
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants administered with ALS-008176 oral-liquid suspension, 375 mg every 12 hours for 5 days (10 doses).

Arm title	ALS-008176: 750 mg LD/150 mg MD

Arm description:

Participants administered with ALS-008176 oral-liquid suspension as a 750 mg loading dose (Dose 1), followed by 150 mg Q12 maintenance doses (Doses 2-10) under fed condition.

Arm type	Experimental
Investigational medicinal product name	ALS-008176
Investigational medicinal product code	
Other name	C12041850-E
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants administered with ALS-008176 as a 750 mg loading dose (Dose 1), followed by 150 mg Q12 maintenance doses (Doses 2-10) orally in the form of suspension.

Number of subjects in period 1	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg
Started	18	14	11
Completed	18	14	11

Number of subjects in period 1	ALS-008176: 750 mg LD/150 mg MD
Started	19
Completed	19

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants administered with Placebo oral solution for every 12 hours.	
Reporting group title	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension as a 750 milligram (mg) loading dose (Dose 1), followed by 500 mg every 12 hours (Q12) maintenance dose (Doses 2-10) under fed condition.	
Reporting group title	ALS-008176: 375 mg
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension, 375 mg every 12 hours for 5 days (10 doses) under fed condition.	
Reporting group title	ALS-008176: 750 mg LD/150 mg MD
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension as a 750 mg loading dose (Dose 1), followed by 150 mg Q12 maintenance doses (Doses 2-10) under fed condition.	

Reporting group values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg
Number of subjects	18	14	11
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	14	11
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
arithmetic mean	24.6	22.4	23.4
standard deviation	± 4.33	± 3.01	± 2.42
Title for Gender			
Units: subjects			
Female	4	4	2
Male	14	10	9

Reporting group values	ALS-008176: 750 mg LD/150 mg MD	Total	
Number of subjects	19	62	
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	62	
From 65 to 84 years	0	0	
85 years and over	0	0	

Title for AgeContinuous Units: years			
arithmetic mean	24.7		
standard deviation	± 6.23	-	
Title for Gender Units: subjects			
Female	7	17	
Male	12	45	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants administered with Placebo oral solution for every 12 hours.	
Reporting group title	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension as a 750 milligram (mg) loading dose (Dose 1), followed by 500 mg every 12 hours (Q12) maintenance dose (Doses 2-10) under fed condition.	
Reporting group title	ALS-008176: 375 mg
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension, 375 mg every 12 hours for 5 days (10 doses) under fed condition.	
Reporting group title	ALS-008176: 750 mg LD/150 mg MD
Reporting group description:	
Participants administered with ALS-008176 oral-liquid suspension as a 750 mg loading dose (Dose 1), followed by 150 mg Q12 maintenance doses (Doses 2-10) under fed condition.	
Subject analysis set title	Dose 1: 750 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with ALS-008176, 750 mg as loading dose orally.	
Subject analysis set title	Dose 2: 150 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 150 mg, ALS-008176 orally for every 12 hours (Q12) maintenance dose.	
Subject analysis set title	Dose 2: 500 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 500 mg, ALS-008176 orally for every 12 hours (Q12) maintenance dose.	
Subject analysis set title	Dose 9/10: 150 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 150 mg, ALS-008176 orally for every 12 hours (Q12) maintenance dose.	
Subject analysis set title	Dose 9/10: 500 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 500 mg, ALS-008176 orally for every 12 hours (Q12) maintenance dose.	
Subject analysis set title	Dose 1: 375 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 375 mg, ALS-008176 orally twice daily (BID).	
Subject analysis set title	Dose 2: 375 milligrams
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants administered with a dose of 375 mg, ALS-008176 orally twice daily (BID).	
Subject analysis set title	Dose 9/10: 375 milligrams

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants administered with a dose of 375 mg, ALS-008176 orally twice daily (BID).

Primary: Reduction in AUC of Respiratory Syncytial Virus (RSV)-A Memphis 37b Viral Load From Baseline Through Study Day 12

End point title	Reduction in AUC of Respiratory Syncytial Virus (RSV)-A Memphis 37b Viral Load From Baseline Through Study Day 12

End point description:

Reduction in Area Under Curve (AUC) of RSV-A Memphis 37b viral load as determined by quantitative Polymerase Chain Reaction (PCR) assay of nasopharyngeal wash. AUC was calculated using log10viral load values. IIT-I population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) with a positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug.

End point type	Primary

End point timeframe:

Baseline through Day 12

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: Log10 PFUe·hour/mL				
arithmetic mean (standard deviation)	500.9 (± 219.9)	59.9 (± 69.5)	133.4 (± 118.4)	73.7 (± 48.3)

Statistical analyses

Statistical analysis title	Statistical analysis-I

Statistical analysis description:

Based on a mixed model adjusted for unequal variances with baseline as a covariate comparing 750 mg LD/500 mg MD to Placebo. Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.

Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis II

Statistical analysis description:

Based on a mixed model adjusted for unequal variances with baseline as a covariate comparing 375 mg MD to Placebo. Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.

Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis III

Statistical analysis description:

Based on a mixed model adjusted for unequal variances with baseline as a covariate comparing 750 mg LD/150 mg MD to Placebo. Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.

Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Time to Non-detectability of Respiratory Syncytial Virus (RSV) Ribo-Nucleic Acid (RNA)

End point title	Time to Non-detectability of Respiratory Syncytial Virus (RSV) Ribo-Nucleic Acid (RNA)

End point description:

Time to non-detectability of virus (RSV-A Memphis 37b) as measured from immediately prior to the first dose of study medication. Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) witha positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug.

End point type	Secondary

End point timeframe:

Day 2 to Day 12

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: days				
arithmetic mean (standard deviation)	7.2 (± 3.1)	1.3 (± 1.3)	2.3 (± 1.5)	1.4 (± 0.5)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.	
Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.	
Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Viral Load Slope

End point title	Viral Load Slope

End point description:

Mean change in Log10 Plasma Human Immunodeficiency Virus (HIV) Viral Load. Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat

[ITT] Population) witha positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to 48 hours post dose

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: (Log10 PFUe/mL)/ hours				
arithmetic mean (standard deviation)				
Baseline to 24 hours post 1st dose (24 hours)	0.6 (± 1.8)	-1.7 (± 1.1)	-0.2 (± 1)	-1.7 (± 1.2)
Baseline to 48 hours post 1st dose (48 hours)	1.1 (± 1)	-1 (± 0.5)	-0.6 (± 0.5)	-1.1 (± 0.9)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.

Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	ANCOVA

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.

Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6555
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0191
Method	ANCOVA

Secondary: Peak RSV Viral Load

End point title	Peak RSV Viral Load
End point description: Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) witha positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug.	
End point type	Secondary
End point timeframe: Up to Day 12	

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: Log10 PFUe/mL				
arithmetic mean (standard deviation)	5.3 (± 1.2)	2.3 (± 1.3)	3.1 (± 1.3)	3.1 (± 1.1)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.	
Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.	
Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Viral Load at 3.5 days post first dose	
End point title	Viral Load at 3.5 days post first dose
End point description: Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) witha positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug.	
End point type	Secondary
End point timeframe: Day 3.5	

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: Log10 PFUe/mL				
arithmetic mean (standard deviation)	4.3 (± 2.1)	0.6 (± 1.1)	0.8 (± 1.4)	0 (± 0.1)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.	
Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANCOVA

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.	
Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: RSV Total Symptom Score AUC Baseline through Study Day 16

End point title	RSV Total Symptom Score AUC Baseline through Study Day 16

End point description:

Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) with a positive quantitative PCR value immediately prior to

treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug. The antiviral effect of oral ALS-008176 compared to placebo will be measured by the mean AUC for the total symptom score and peak change from baseline (immediately prior to the first dose of IMP) in total RSV-A symptoms from immediately prior to the first dose of IMP until Study Day 16 and from immediately prior to the first dose of IMP the last measurement until Study Day 16. Time days by treatment groups.

End point type	Secondary

End point timeframe:

Up to Day 16

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	8	7
Units: hours				
arithmetic mean (standard deviation)	606.9 (± 564.8)	111.7 (± 94)	113.1 (± 110.3)	73.2 (± 63.4)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.

Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117
Method	ANCOVA

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.

Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0075
Method	ANCOVA

Secondary: Mucus Weight AUC Baseline through Study Day 12

End point title	Mucus Weight AUC Baseline through Study Day 12
End point description:	
Intent to Treat-Infected (ITT-I) population defined as all subjects receiving Challenge Virus and IMP (i.e., the Intent-to-Treat [ITT] Population) witha positive quantitative PCR value immediately prior to treatment (or) any subject who was quantitative PCR negative prior to treatment who subsequently had two or more quantitative PCR positive values after the first dose of study drug. Analyses performed using an analysis of variance (ANOVA) model included mucus weight over time and change from baseline in mucus weight over time.	
End point type	Secondary
End point timeframe:	
Day 2 to Day 12	

End point values	Placebo	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD	ALS-008176: 375 mg	ALS-008176: 750 mg LD/150 mg MD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	7	8
Units: Gram*Day				
arithmetic mean (standard deviation)	18.6 (± 18.4)	3 (± 2)	5.4 (± 7.6)	5.9 (± 6.3)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Number of subjects included in analysis was 12 for Placebo and 8 for 750 mg LD/500 mg MD.	
Comparison groups	ALS-008176: 750 mg Loading Dose (LD)/500 mg MD v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203
Method	ANCOVA

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 8 for 375 mg.	
Comparison groups	ALS-008176: 375 mg v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0581
Method	ANCOVA

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Number of subjects included in analysis was 12 for Placebo and 7 for 750 mg LD/150 mg MD.	
Comparison groups	ALS-008176: 750 mg LD/150 mg MD v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0869
Method	ANCOVA

Secondary: Maximum Plasma Concentration (Cmax)	
End point title	Maximum Plasma Concentration (Cmax)
End point description: The C max is the maximum serum concentration which was observed at the defined time point. Pharmacokinetic analysis set population included all ITT subjects who had at least one PK specimen.	
End point type	Secondary
End point timeframe: Up to day 12	

End point values	Dose 1: 750 milligrams	Dose 2: 150 milligrams	Dose 2: 500 milligrams	Dose 9/10: 150 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	19	14	19
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
ALS-008112	1736.4 (± 700.3)	468.6 (± 180.8)	1234.3 (± 578.6)	600.9 (± 210.5)
ALS-008144	98.82 (± 47.77)	36.94 (± 18.92)	80.49 (± 37.13)	53.63 (± 17.3)

End point values	Dose 9/10: 500 milligrams	Dose 1: 375 milligrams	Dose 2: 375 milligrams	Dose 9/10: 375 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	11	11	11
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
ALS-008112	1665.7 (± 528.1)	1155.5 (± 554.6)	933 (± 304.5)	1581.4 (± 485.2)
ALS-008144	142.77 (± 54.21)	46.31 (± 25.85)	51.49 (± 22.84)	119.27 (± 33.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Plasma Concentration (Tmax)

End point title	Time to Reach the Maximum Plasma Concentration (Tmax)

End point description:

The Tmax is time to reach the observed maximum plasma concentration. Pharmacokinetic analysis set population included all ITT subjects who had at least one PK specimen.

End point type	Secondary

End point timeframe:

Up to day 12

End point values	Dose 1: 750 milligrams	Dose 2: 150 milligrams	Dose 2: 500 milligrams	Dose 9/10: 150 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	19	14	19
Units: Hour (h)				
median (full range (min-max))				
ALS-008112	1 (0.25 to 6)	0.533 (0.25 to 2.02)	1 (0.25 to 4)	0.5 (0.25 to 2)
ALS-008144	2 (1 to 6)	2 (0.5 to 4)	2 (0.5 to 4)	1 (0.5 to 4)

End point values	Dose 9/10: 500 milligrams	Dose 1: 375 milligrams	Dose 2: 375 milligrams	Dose 9/10: 375 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	11	11	11
Units: Hour (h)				
median (full range (min-max))				
ALS-008112	1 (0.25 to 2.08)	0.5 (0.25 to 2)	0.5 (0.3 to 4)	0.5 (0.25 to 1.07)
ALS-008144	2 (0.5 to 2.08)	1 (0.5 to 6)	1.983 (0.5 to 4)	1.05 (0.5 to 2.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to twelve hours Time (AUC [0-12 h])

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to twelve hours Time (AUC [0-12 h])

End point description:

The AUC (0-12 h) is the area under the plasma concentration-time curve from time zero to time of the 12 hours observed quantifiable concentration. Pharmacokinetic analysis set population included all ITT subjects who had at least one PK specimen.

End point type	Secondary

End point timeframe:

Up to day 12

End point values	Dose 1: 750 milligrams	Dose 2: 150 milligrams	Dose 2: 500 milligrams	Dose 9/10: 150 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	19	14	19
Units: nanogram*hour per millilitre (ng.h/mL)				
arithmetic mean (standard deviation)				
ALS-008112	5915.6 (± 1437.4)	1660.7 (± 259.5)	4056.5 (± 1105.8)	1782.9 (± 260.4)
ALS-008144	522.5 (± 234.48)	261.77 (± 66.93)	476.08 (± 153.7)	388 (± 91)

End point values	Dose 9/10: 500 milligrams	Dose 1: 375 milligrams	Dose 2: 375 milligrams	Dose 9/10: 375 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	11	11	11
Units: nanogram*hour per millilitre (ng.				

h/mL)				
arithmetic mean (standard deviation)				
ALS-008112	5397.1 (± 877.5)	2707.6 (± 584.5)	2973.4 (± 466.1)	4298.7 (± 570.4)
ALS-008144	1011.21 (± 258.22)	208.67 (± 87.83)	299.1 (± 80.13)	783.72 (± 129.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to twenty four hours Time (AUC [0-24 h])

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to twenty four hours Time (AUC [0-24 h])

End point description:

The AUC (0-24 h) is the area under the plasma concentration-time curve from time zero to time of the 24 hours observed in quantifiable concentration. Pharmacokinetic analysis set population included all ITT subjects who had at least one PK specimen.

End point type	Secondary

End point timeframe:

Up to day 12

End point values	Dose 2: 150 milligrams	Dose 2: 500 milligrams	Dose 9/10: 150 milligrams	Dose 9/10: 500 milligrams
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	14	19	14
Units: nanogram*hour per millilitre (ng.h/mL)				
arithmetic mean (standard deviation)				
ALS-008112	7762.9 (± 1892.5)	9718.8 (± 1897.1)	3565.8 (± 520.8)	10794.2 (± 1754.9)
ALS-008144	798.99 (± 322.84)	978.62 (± 335.35)	776 (± 181.99)	2022.42 (± 516.44)

End point values	Dose 2: 375 milligrams	Dose 9/10: 375 milligrams		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: nanogram*hour per millilitre (ng.h/mL)				
arithmetic mean (standard deviation)				
ALS-008112	5681 (± 820.3)	8597.3 (± 1140.8)		
ALS-008144	507.77 (± 153.49)	1567.44 (± 258.65)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to follow-up (Day 28)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants administered with Placebo oral solution for every 12 hours.	
Reporting group title	ALS-008176: 750 mg LD/500 mg MD
Reporting group description: Participants administered with ALS-008176 oral-liquid suspension as a 750 milligram (mg) loading dose (Dose 1), followed by 500 mg every 12 hours (Q12) maintenance dose (Doses 2-10).	
Reporting group title	ALS-008176: 375 mg
Reporting group description: Participants administered with ALS-008176 oral-liquid suspension, 375 mg every 12 hours for 5 days (10 doses) under fed condition.	
Reporting group title	ALS-008176: 750 mg LD/150 mg MD
Reporting group description: Participants administered with ALS-008176 oral-liquid suspension as a 750 mg loading dose (Dose 1), followed by 150 mg Q12 maintenance doses (Doses 2-10).	

Serious adverse events	Placebo	ALS-008176: 750 mg LD/500 mg MD	ALS-008176: 375 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	ALS-008176: 750 mg LD/150 mg MD		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	ALS-008176: 750 mg LD/500 mg MD	ALS-008176: 375 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	10 / 14 (71.43%)	9 / 11 (81.82%)
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter Site Related Reaction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 18 (5.56%)	2 / 14 (14.29%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Epistaxis			
subjects affected / exposed	2 / 18 (11.11%)	4 / 14 (28.57%)	1 / 11 (9.09%)
occurrences (all)	2	4	1
Nasal Congestion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Sneezing			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 18 (16.67%)	3 / 14 (21.43%)	2 / 11 (18.18%)
occurrences (all)	3	3	2
Aspartate Aminotransferase Increased			
subjects affected / exposed	2 / 18 (11.11%)	2 / 14 (14.29%)	0 / 11 (0.00%)
occurrences (all)	2	2	0
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Blood Uric Acid Increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood Urine Present			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
C-Reactive Protein			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Culture Urine Positive			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Platelet Count Decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			

Joint Dislocation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ligament Sprain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Aphthous Stomatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

Mouth Ulceration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 18 (5.56%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Otitis Externa			
subjects affected / exposed	0 / 18 (0.00%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 18 (11.11%)	1 / 14 (7.14%)	0 / 11 (0.00%)
occurrences (all)	2	1	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	ALS-008176: 750 mg LD/150 mg MD		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	15 / 19 (78.95%)		
Vascular disorders			
Orthostatic Hypotension			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Catheter Site Related Reaction			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Nasal Congestion			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Oropharyngeal Pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Blood Thyroid Stimulating Hormone Increased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Blood Uric Acid Increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood Urine Present			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
C-Reactive Protein			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Culture Urine Positive			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Platelet Count Decreased			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Joint Dislocation			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Ligament Sprain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Aphthous Stomatitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Mouth Ulceration			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Impetigo			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Otitis Externa			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2013	The overall reason for the amendment was to include the definitions for suspension of treatment were revised, requiring fewer adverse events to satisfy the criteria, If a dose level was suspended and comprehensive review conducted, the provision to continue treatment at that dose level or repeat that dose level was removed and study drug packaging was revised to allow for the use of amber syringes covered with aluminum foil overlaid with the drug label.
30 January 2014	The overall reason for the amendment was to include the viral challenge model to more closely emulate clinical RSV disease, The first modification allowed initiation of treatment up to 3 days after subjects were found to be Polymerase Chain Reaction (PCR) positive by nasopharyngeal wash. This longer time window was more analogous to the time window that will be seen in clinical practice, where patients do not usually present to their doctors until symptoms have occurred, typically around Day 3 of infection, The second modification to the protocol allowed for treatment of subjects for up to 9 days. This revision was considered important in the event that data from study period 1 suggested the 5-day treatment duration was insufficient. This less than or equal (< =) to 9-day treatment duration remains shorter than the 14-day treatment duration previously evaluated in the healthy volunteer SAD/MAD study, which was found to be well tolerated. The safety profile of ALS-008176 was also updated to include adverse events experienced by healthy volunteers treated for 14 days to further support this change, Inclusion of recently available proof-of-concept data from an African Green monkey RSV infection model, Removal of plaque assay analysis at Days 16 and 28, Addition of a provision for dose administration via single use amber glass bottles, Editorial changes for consistency within the document.
14 May 2014	The overall reason for the amendment was to include the The rate of infection in the study was anticipated to be < 70 percent (%). An additional study period (study period 4) with a slightly larger size (N = 24) was added because it would provide additional infected subject data which will further enhance the statistical assessment of the efficacy and PK-PD properties of ALS-008176. In the event that a full study period could not be enrolled in a timely fashion, the added language allowed the possibility to enroll the additional 24 subjects across multiple study periods, Additional changes and clarifications included The protocol already provided for once daily treatment after conduct of study period 1. Further editorial changes were made to assure consistency across the document, Existing antiviral parameters were clarified and additional antiviral parameters (as determined by qPCR of nasal wash) including change in viral load over time; change in AUC0-t over different time periods; time to non-detectability of virus from commencement of study medication; peak viral load and time to peak viral load; and proportion of subjects with detectable virus by time following commencement of study medication) were introduced to aid in analysis of efficacy and PK-PD. Similar antiviral endpoints may have been evaluated based on quantitative culture (tissue infectivity plaque assays), Increased the total number of subjects that could be enrolled, clarification that O2 saturation will not be assessed as clinically warranted, at the physician's discretion, clarification of the timing of Day 1 safety laboratories, clarification of nasal swab tolerability testing, potential analyses of inflammatory markers and added text identifying Triangle Biostatistics as the statistical analysis vendor and provides updates to harmonize the protocol with the SAP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported